

Substitute PTO/SB/8A (08-00)

Approved for use through 10/31/2002. OMB 0651-0031

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

<b>Substitute for form 1449A/PTO (Modified)</b>  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)				<b>Complete if Known</b>	
				Application Number	10/000,433
				Filing Date	November 30, 2001
				First Named Inventor	TOMIZUKA, Kazuma
				Group Art Unit	
				Examiner Name	
Sheet	1	of	7	Attorney Docket Number	014643-012110US (A-72018/455675-83)

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.	U.S. Patent Document Number-Kind Code <sup>2</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	5,175,384	12-1992	Krimpenfort	
	A2	5,204,244	04-1993	Fell et al.	
	A3	5,416,260	05-1995	Jikker	
	A4	5,434,340	07-1995	Krimpenfort	
	A5	5,545,806	08-1996	Lonberg et al.	
	A6	5,545,807	08-1996	Surani	
	A7	5,569,825	10-1996	Lonberg et al.	
	A8	5,625,126	04-1997	Lonberg et al.	
	A9	5,633,425	05-1997	Lonberg et al.	
	A10	5,661,016	08-1997	Lonberg et al.	
	A11	5,698,196	12-1997	Matsushima	
	A12	5,702,946	12-1997	Doerschuk	
	A13	5,770,429	06-1998	Lonberg et al.	
	A14	5,789,650	08-1998	Lonberg et al.	
	A15	5,814,318	09-1998	Lonberg et al.	
	A16	5,939,598	08-1999	Kuchertapati et al.	
	A17	5,874,299	02-1999	Lonberg et al.	
	A18	5,877,397	03-1999	Lonberg et al.	
	A19	6,300,129	10-2001	Lonberg et al.	

RECEIVED  
MAY 19 2003  
TECH CENTER 1600/2000

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.	Foreign Patent Document Country Code <sup>2</sup> Number <sup>4</sup> Kind Code <sup>5</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>6</sup>
	B1	EP 0 315 062 ✓	05-1989			
	B2	WO 90/04036 ✓	04-1990			
	B3	WO 90/12878 ✓	11-1990			
	B4	WO 91/00906 ✓	01-1991			
	B5	WO 91/10741 ✓	07-1991			
	B6	WO 92/03918 ✓	03-1992			
	B7	WO 96/02576 ✓	02-1996			

Examiner Signature		Date Considered	6/3/05
--------------------	--	-----------------	--------

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English Language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. 1109726\_1



Substitute PTO/SB/8A (08-00)  
Approved for use through 10/31/2002. OMB 0651-0031  
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE  
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO (Modified)		<b>Complete if Known</b>			
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)		Application Number	10/000,433		
		Filing Date	November 30, 2001		
		First Named Inventor	TOMIZUKA, Kazuma		
		Group Art Unit			
		Examiner Name			
Sheet	2	of	7	Attorney Docket Number	014643-012110US (A-72018/455675-3)

### OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	
✓	C1	ALT, F.W., et al., "Immunoglobulin genes in transgenic mice", <i>Trends in Genetics</i> , 231-236, (Aug. 1985).	
✓	C2	BERMAN, J.E., et al., "Content and organization of the human Ig V <sub>H</sub> locus: definition of three new V <sub>H</sub> families and linkage to the Ig C <sub>H</sub> locus", <i>The EMBO J.</i> 7:727-738 (1988).	
✓	C3	BERTON, M.T., et al., "Synthesis of germ-line $\gamma$ 1 immunoglobulin heavy-chain transcripts in resting B cells: Induction by interleukin 4 and inhibition by interferon $\gamma$ ", <i>Proc. Natl. Acad. Sci. (U.S.A.)</i> 86:2829-2833 (1989).	
✓	C4	BOLLAG, R.J., et al., "Homologous recombination in mammalian cells", <i>Annu. Rev. Genet.</i> 23:199-225 (1989).	
✓	C5	BRUGGEMANN, M., et al., "A repertoire of monoclonal antibodies with human heavy chains from transgenic mice", <i>Proc. Natl. Acad. Sci. USA</i> 86:6709-6713 (1989).	
✓	C6	BRUGGEMANN, M., et al., "Human antibody production in transgenic mice: expression from 100 kb of the human IgH locus", <i>Eur. J. Immunol.</i> 21:1323-1326 (1991).	
✓	C7	BUCCHINI, D., et al., "Rearrangement of a chicken immunoglobulin gene occurs in the lymphoid lineage of transgenic mice", <i>Nature</i> 326:409-411 (1987).	
✓	C8	BUTTIN, G., "Exogenous Ig gene rearrangement in transgenic mice: a new strategy for human monoclonal antibody production?" <i>Trends in Genetics</i> --vol. 3, No. 8, 205-206 (Aug. 1987).	
✓	C9	CAPECCHI, M.R., "Altering the genome by homologous recombination", <i>Science</i> 244:1288-1292 (1989).	
✓	C10	CAPECCHI, M.R., "The new mouse genetics: Altering the genome by gene targeting", <i>Trends in Genetics</i> 5:70-76 (1989).	
✓	C11	CHOI, T.K., et al., "Transgenic mice containing a human heavy chain immunoglobulin gene fragment cloned in a yeast artificial chromosome." <i>Nat. Genet.</i> 1993 Jun;4(2):117-23.	
✓	C12	COFFMAN, R.L., et al., "A mouse T cell product that preferentially enhances IgA production", <i>J. Immunol.</i> 139:3685-3690 (1987).	
✓	C13	COFFMAN, R.L., and CARTY, J., "A T cell activity that enhances polyclonal IgE production and its inhibition by interferon- $\gamma$ ", <i>J. Immunol.</i> 136:949-954 (1986).	
✓	C14	DAVIES, N.P., et al., "Creation of Mice Expressing Human Antibody Light Chains by Introduction of a Yeast Artificial Chromosome Containing the Core Region of the Human Immunoglobulin $\kappa$ Locus." <i>Biotechnology (N Y)</i> . 1993 Aug;11(8):911-4.	
✓	C15	DAVIES, N.P., et al., "Targeted Alterations in Yeast Artificial Chromosomes for Inter-Species Gene Transfer", <i>Nucleic Acid Res.</i> 20: 2693-2698 (1992).	
✓	C16	DOETSCHMAN, T., et al., "Targetted correction of a mutant HPRT gene in mouse embryonic stem cells", <i>Nature</i> 330:576-578 (1987).	
✓	C17	DURDIK, J., et al., "Isotype switching by a microinjected $\mu$ immunoglobulin heavy chain gene in transgenic mice", <i>Proc. Natl. Acad. Sci. USA</i> 86:2346-2350 (1989).	
✓	C18	ESSER, C., and RADBRUCH, A., "Rapid induction of transcription of unrearranged Sy1 switch regions in activated murine B cells by interleukin 4", <i>The EMBO J.</i> 8:483-488 (1989).	
✓	C19	FERRIER, P., et al., "Separate elements control DJ and VDJ rearrangement in a transgenic recombination substrate", <i>The EMBO J.</i> 9:117-125 (1990).	

Examiner Signature		Date Considered	6/3/05
--------------------	--	-----------------	--------

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English Language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. 1109726\_1



Substitute PTO/SB/8A (08-00)  
Approved for use through 10/31/2002. OMB 0651-0031  
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE  
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO (Modified)		<b>Complete if Known</b>			
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)		Application Number	10/000,433		
		Filing Date	November 30, 2001		
		First Named Inventor	TOMIZUKA, Kazuma		
		Group Art Unit			
		Examiner Name			
Sheet	3	of	7	Attorney Docket Number	014643-012110US (A-72018/455675-83)

RECEIVED  
MAY 30 2003  
TECH CENTER 1800/2800

### OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	
✓	C20	FISHWILD, D.M., et al. "High-Avidity human IgGx monoclonal antibodies from a novel strain of minilocus transgenic mice", <i>Nature Biotechnology</i> 14:845. (1996).	✓
✓	C21	FORNI, L., "Extensive splenic B cell activation in IgM-transgenic mice", <i>Eur. J. Immunol.</i> 20:983-989 (1990).	
✓	C22	GERSTEIN, R.M., et al., "Isotype Switching of an Immunoglobulin Heavy Chain Transgene Occurs by DNA Recombination between Different Chromosomes", <i>Cell</i> 63:537-548 (1990).	
✓	C23	GOODHARDT, M., et al., "Rearrangement and expression of rabbit immunoglobulin $\kappa$ light chain gene in transgenic mice", <i>Proc. Natl. Acad. Sci. (U.S.A.)</i> 84:4229-4233 (1987).	
	C24	GORDON, J., "Transgenic mice in immunology", <i>The Mount Sinai Journal of Medicine</i> , 53:223-231 (1986).	
✓	C25	GREEN, L.L., et al., "Antigen-specific human monoclonal antibodies from mice engineered with human Ig heavy and light chain YACs", <i>Nature Genetics</i> 7:13-21 (1994).	
✓	C26	HAGMAN, J., et al., "Inhibition of immunoglobulin gene rearrangement by the expression of a $\lambda 2$ transgene", <i>J. Exp. Med.</i> 169:1911-1929 (1989).	
✓	C27	HOFKER, M.H., et al., "Complete physical map of the human immunoglobulin heavy chain constant region gene complex", <i>Proc. Natl. Acad. Sci. USA</i> 86:5567-5571 (1989).	
✓	C28	HUMPHRIES, C.G., et al., "A new human immunoglobulin $V_H$ family preferentially rearranged in Immature B-cell tumours", <i>Nature</i> 331:446-449 (1988).	
✓	C29	HUXLEY, C., et al., "The human HPRT gene on a yeast artificial chromosome is functional when transferred to mouse cells by cell fusion." <i>Genomics</i> 1991 Apr;9(4):742-50.	
✓	C30	ICHIHARA, Y., et al., "Organization of human immunoglobulin heavy chain diversity gene loci", <i>The EMBO J.</i> 7:4141-4150 (1988).	
✓	C31	IGLESIAS, A., et al., "Expression of immunoglobulin delta chain causes allelic exclusion in transgenic mice", <i>Nature</i> 330:482-484 (1987).	
✓	C32	JAENISCH, R., "Transgenic Animals", <i>Science</i> 240:1468-1474 (1988).	
	C33	JAKOBOVITS, A., et al., "Analysis of homozygous mutant chimeric mice: Deletion of the immunoglobulin heavy-chain joining region blocks B-cell development and antibody production", <i>Proc. Natl. Acad. Sci. USA</i> 90:2551-2555 (1993).	
✓	C34	JAMES, K., and BELL, G.T., "Human monoclonal antibody production current status and future prospects", <i>J. of Immunol. Methods</i> 100:5-40 (1987).	
✓	C35	JASIN, M., and BERG, P., "Homologous integration in mammalian cells without target gene selection", <i>Genes &amp; Development</i> 2:1353-1363 (1988).	
✓	C36	JUNG, S., et al., "Shutdown of Class Switching Recombination by Deletion of a Switch Region Control Element", <i>Science</i> 259:984-987 (1993).	
✓	C37	KENNY, J.J., et al., "Alteration of the B cell surface phenotype, immune response to phosphocholine and the B cell repertoire in M167 $\mu$ plus $\kappa$ transgenic mice", <i>J. of Immunol.</i> 142:4466-4474 (1989).	
✓	C38	KITAMURA, D., et al., "A B cell-deficient mouse by targeted disruption of the membrane exon of the immunoglobulin $\mu$ chain gene", <i>Nature</i> 350:423-426 (1991).	

Examiner Signature		Date Considered	6/3/05
-----------------------	--	--------------------	--------

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English Language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. 1109726\_1



Substitute for form 1449A/PTO (Modified)			<b>Complete if Known</b>		
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)			Application Number	10/000,433	
			Filing Date	November 30, 2001	
			First Named Inventor	TOMIZUKA, Kazuma	
			Group Art Unit		
			Examiner Name		
Sheet	4	of	7	Attorney Docket Number	014643-012110US (A-72018/455675-83)

RECEIVED  
MAY 18 2003  
TECH CENTER  
1600/2900

**OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS**

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	1*
✓	C39	KOLLER, B.H., and SMITHIES, O., "Inactivating the $\beta_2$ -microglobulin locus in mouse embryonic stem cells by homologous recombination", <i>Proc. Natl. Acad. Sci. USA</i> 86:8932-8935 (1989).	
✓	C40	LIN, F.L., et al., "Recombination in mouse L cells between DNA introduced into cells and homologous chromosomal sequences", <i>Proc. Natl. Acad. Sci. USA</i> 82:1391-1395 (1985).	
✓	C41	LINTON, P.-J., et al., "Primary Antibody-Forming Cells and Secondary B Cells Are Generated from Separate Precursor Cell Subpopulations", <i>Cell</i> 59:1049-1059 (1989).	
✓	C42	LO, D., et al., "Expression of mouse IgA by transgenic mice, pigs and sheep", <i>Eur. J. Immunol.</i> 21:1001-1006 (1991).	
✓	C43	LONBERG, M., et al., "Antigen-specific human antibodies from mice comprising four distinct genetic modifications", <i>Nature</i> 368:856-859 (1994).	
✓	C44	LORENZ, W., et al., "Physical map of the human immunoglobulin $\kappa$ locus and its implications for the mechanisms of $V_{\kappa}$ - $J_{\kappa}$ rearrangement", <i>Nucl. Acids Res.</i> 15:9667-9676 (1987).	
✓	C45	LUTZKER, S., and ALT, F.W., "Structure and Expression of Germ Line Immunoglobulin $\gamma 2b$ Transcripts", <i>Mol. Cell Biol.</i> 8:1849-1852 (1988).	
✓	C46	MANSOUR, S.L., et al., "Disruption of the proto-oncogene <i>int-2</i> in mouse embryo-derived stem cells: a general strategy for targeting mutations to non-selectable genes", <i>Nature</i> 336:348-352 (1988).	
✓	C47	MILLER, J., et al., "Structural alterations in J regions of mouse immunoglobulin $\lambda$ genes are associated with differential gene expression", <i>Nature</i> 295:428-430 (1982).	
✓	C48	MILLS, F.C., et al., "DNase I hypersensitive sites in the chromatin of human $\mu$ immunoglobulin heavy-chain genes", <i>Nature</i> 306:809-812 (1983).	
✓	C49	MILLS, F.C., et al., "Sequences of human immunoglobulin switch regions: implications for recombination and transcription", <i>Nucl. Acids. Res.</i> 18:7305-7316 (1991).	
✓	C50	MORRISON, S.L., "Success in specification", <i>Nature</i> 368:812-813 (1994).	
✓	C51	MOWATT, M.R., et al., "DNA sequence of the murine $\gamma 1$ switch segment reveals novel structural elements", <i>J. Immunol.</i> 136:2674-2683 (1986).	
✓	C52	MÜLLER, W., et al., "Membrane-bound IgM obstructs B cell development in transgenic mice", <i>Eur. J. Immunol.</i> 19:923-928 (1989).	
✓	C53	MURRAY, A.W., and SZOSTAK, J.W., "Construction of artificial chromosomes in yeast", <i>Nature</i> 305:189-193 (1983).	
✓	C54	NIKAIDO, T., et al., "Nucleotide Sequences of Switch Regions of Immunoglobulin C and C Genes and Their Comparison", <i>J. Biol. Chem.</i> 257:7322-7239 (1982).	
✓	C55	NIKAIDO, T., et al., "Switch region of immunoglobulin $C_{\mu}$ gene is composed of simple tandem repetitive sequences", <i>Nature</i> 292:845-848 (1981).	
✓	C56	NEUBERGER, M.S., et al., "Isotype exclusion and transgene down-regulation in immunoglobulin- $\lambda$ transgenic mice", <i>Nature</i> 338:350-352 (1989).	
✓	C57	NEUBERGER, M.S., "Generating high-avidity human Mabs in mice", <i>Nature Biotechnology</i> 14:826 (1996).	
✓	C58	NUSSENZWEIG, M.C., et al., "Allelic exclusion in transgenic mice carrying mutant human IgM genes", <i>J. Exp. Med.</i> 167:1969 (1988).	

Examiner Signature		Date Considered	6/3/05
--------------------	--	-----------------	--------

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 809. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English Language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. 1109726\_1



Substitute PTO/SB/8A (08-00)  
Approved for use through 10/31/2002. OMB 0851-0031  
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE  
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

<b>Substitute for form 1449/APTO (Modified)</b>  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)		<b>Complete if Known</b>			
		Application Number	10/000,433		
		Filing Date	November 30, 2001		
		First Named Inventor	TOMIZUKA, Kazuma		
		Group Art Unit	1632		
Examiner Name	LI, Q. Janice				
Sheet	2	of	2	Attorney Docket Number	014643-012110US/ A-72018/GKS/THR

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner Initials	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>2</sup>
<input checked="" type="checkbox"/>	C115	KAZUKI, Y., et al., "Germline transmission of a transferred human chromosome 21 fragment in transchromosomal mice," <i>J. Hum. Genet.</i> 46(10):600-603 (2001).	
<input type="checkbox"/>	C116	KUROIWA, Y., et al., "Cloned transchromosomal calves producing human immunoglobulin," <i>Nat. Biotechnol.</i> 20(9):889-894 (Sep. 2002).	
<input type="checkbox"/>	C117	KUROIWA, Y., et al., "Efficient modification of a human chromosome by telomere-directed truncation in high homologous recombination-proficient chicken DT40 cells," <i>Nucleic Acid Res.</i> 26(14):3447-3448 (Jul. 1998).	
<input type="checkbox"/>	C118	KUROIWA, Y., et al., "Manipulation of human minichromosomes to carry greater than megabase-sized chromosome inserts," <i>Nat. Biotechnol.</i> 18(10):1086-1090 (Oct. 2000).	
<input type="checkbox"/>	C118	KUROIWA, Y., et al., "The use of chromosome-based vectors for animal transgenesis," <i>Gene Ther.</i> 9(11):708-712 (Jun. 2002).	
<input type="checkbox"/>	C120	ROBL, J.M., et al., "Artificial chromosome vectors and expression of complex proteins in transgenic animals," <i>Theriogenology</i> 59:107-113 (2003).	
<input type="checkbox"/>	C121	SANO, T., et al., "Transgenic potato expressing a double-stranded RNA-specific ribonuclease is resistant to potato spindle tuber viroid," <i>Nat. Biotechnol.</i> 15(12):1290-1294 (Nov. 1997).	
<input checked="" type="checkbox"/>	C122	SHINOHARA, T., et al., "Stability of transferred human chromosome fragments in cultured cells and in mice," <i>Chromosome Res.</i> 8(8):713-725 (2000).	
<input type="checkbox"/>	C123	TOMIZUKA, K., et al., "Double trans-chromosomal mice: Maintenance of two individual human chromosome fragments containing Ig heavy and $\kappa$ loci and expression of fully human antibodies," <i>Proc. Natl. Acad. Sci. USA</i> 97(2):722-727 (Jan. 2000).	
<input type="checkbox"/>	C124	TOMIZUKA, K., et al., "Functional expression and germline transmission of a human chromosome fragment in chimeric mice," <i>Nat. Genet.</i> 16(2):134-143 (Jun. 1997).	
<input checked="" type="checkbox"/>	C125	VON BOEHMER, et al., "Early expression of a T-cell receptor $\beta$ -chain transgene suppresses rearrangement of the V $\gamma$ 4 gene segment," <i>Proc. Natl. Acad. Sci. USA</i> 85(24):9729-9732 (Dec. 1988).	

6/3/05

Examiner Signature		Date Considered	6/3/05
--------------------	--	-----------------	--------

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents at www.uspto.gov or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English Language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. 1123956\_1

UIPE  
MAY 15 2003

Substitute PTO/SB/8A (08-00)

Approved for use through 10/31/2002. OMB 0651-0031  
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO (Modified)			<b>Complete if Known</b>		
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)			Application Number	10/000,433	
			Filing Date	November 30, 2001	
			First Named Inventor	TOMIZUKA, Kazuma	
			Group Art Unit		
			Examiner Name		
Sheet	5	of	7	Attorney Docket Number	014643-012110US (A-72018/455675-83)

### OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	†
✓	C59	NUSSENZWEIG, M.C., et al., "A human immunoglobulin gene reduces the incidence of lymphomas in c-Myc-bearing transgenic mice", <i>Nature</i> 336:446-450 (1988).	
✓	C60	OETTINGER, M.A., et al., "RAG-1 and RAG-2, Adjacent Genes That Synergistically Activate V(D)J Recombination", <i>Science</i> 248:1517-1523 (1990).	
✓	C61	PETTERS, R.M., "Transgenic mice in immunological research", <i>Vet. Immunol. Immunopath.</i> 17:267-278 (1987).	
✓	C62	PETTERSSON, S., et al., "A second B cell-specific enhancer 3' of the immunoglobulin heavy-chain locus", <i>Nature</i> 344:165-168 (1990).	
✓	C63	RABBITTS, T.H., et al., "Human immunoglobulin heavy chain genes: evolutionary comparisons of C $\mu$ , C $\delta$ and C $\gamma$ genes and associated switch sequences", <i>Nucl. Acids Res.</i> 9:4509-4524 (1981).	
✓	C64	RATH, S., et al., "B cell abnormalities induced by a $\mu$ Ig transgene extend to L chain isotype usage", <i>J. of Immunol.</i> 146:2841 (1991).	
✓	C65	RATH, S., et al., "Quantitative analysis of idiotypic mimicry and allelic exclusion in mice with a $\mu$ Ig Transgene", <i>J. of Immunol.</i> 143:2074-2080 (1989).	
✓	C66	RAVETCH, J.V., et al., "Evolutionary approach to the question of immunoglobulin heavy chain switching: Evidence from cloned human and mouse genes", <i>Proc. Natl. Acad. Sci. (U.S.A.)</i> 77:6734-6738 (1980).	
✓	C67	REID, L.E., et al., "A single DNA response element can confer inducibility by both $\alpha$ - and $\gamma$ -interferons", <i>Proc. Natl. Acad. Sci. (U.S.A.)</i> 86:840-844 (1989).	
✓	C68	RITCHIE, K.A., et al., "Allelic exclusion and control of endogenous immunoglobulin gene rearrangement in $\kappa$ transgenic mice", <i>Nature</i> 312:517-520 (1984).	
✓	C69	ROTHMAN, P., et al., "Structure and expression of germline immunoglobulin $\gamma$ 3 heavy chain gene transcripts: implications for mitogen and lymphokine directed class-switching", <i>Intl. Immunol.</i> 2:621-627 (1990).	
✓	C70	RUSCONI, S., et al., "Transmission and expression of a specific pair of rearranged immunoglobulin $\mu$ and $\kappa$ genes in a transgenic mouse line", <i>Nature</i> 314:330-334 (1985).	
✓	C71	SATO, T., et al., "Physical linkage of a variable region segment and the joining region segment of the human immunoglobulin heavy chain locus", <i>Biochem. Biophys. Res. Comm.</i> 154:264-271 (1988).	
✓	C72	SCANGOS, G., and BIEBERICH, C., "Gene transfer into mice", <i>Advances in Genetics</i> 24: 285-322 (1987).	
✓	C73	SEVIDY, J.M., and SHARP, P.A., "Positive genetic selection for gene disruption in mammalian cells by homologous recombination", <i>Proc. Natl. Acad. Sci. USA</i> 86:227-231 (1989).	
	C74	SHIMIZU, A., et al., "Immunoglobulin double-isotype expression by trans-mRNA in a human immunoglobulin transgenic mouse", <i>Proc. Natl. Acad. Sci. USA</i> 86:8020-8023 (1989).	
✓	C75	SHIMIZU, A., et al., "Trans-Splicing as a Possible Molecular Mechanism for the Multiple Isotype Expression of the Immunoglobulin Gene", <i>J. Exp. Med.</i> 173:1385-1393 (1991).	
✓	C76	SHIN, E. K., et al., "Physical Map of the 3' Region of the Human Immunoglobulin Heavy Chain Locus: Clustering of Autoantibody-related Variable Segments in One Haplotype", <i>The EMBO J.</i> : 10, 3641-3645 (1991).	
	C77	SIDERAS, P., et al., "Production of sterile transcripts by C $\gamma$ genes in an IgM-producing human neoplastic B cell line that switches to IgG-producing cells", <i>Intl. Immunol.</i> 1: 631-642 (1989).	
	C78	SIEBENLIST, U., et al., "Human immunoglobulin D segments encoded in tandem multigenic families", <i>Nature</i> 294:631-635 (1981).	

Examiner Signature		Date Considered	6/3/05
--------------------	---	-----------------	--------

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 18 if possible. <sup>6</sup> Applicant is to place a check mark here if English Language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. 1109726\_1





Substitute PTO/SB/8A (08-00)

Approved for use through 10/31/2002. OMB 0651-0031

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO (Modified)				<b>Complete if Known</b>	
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)				Application Number	10/000,433
				Filing Date	November 30, 2001
				First Named Inventor	TOMIZUKA, Kazuma
				Group Art Unit	
				Examiner Name	
Sheet	6	of	7	Attorney Docket Number	014643-012110US (A-72018/455675-83)

**OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS**

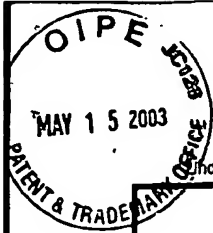
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>1</sup>
✓	C79	SMITHIES, O., et al., "Insertion of DNA sequences into the human chromosomal $\beta$ -globin locus by homologous recombination", <i>Nature</i> 317:230-234 (1985).	
✓	C80	SNAPPER, C.M., and Paul, W.E., "Interferon- $\gamma$ and B Cell Stimulatory Factor-1 Reciprocally Regulate Ig Isotype Production", <i>Science</i> 236:944-947 (1987).	
✓	C81	SONG, K.-Y., et al., "Accurate modification of a chromosomal plasmid by homologous recombination in human cells", <i>Proc. Natl. Acad. Sci. USA</i> 84:6820-6824 (1987).	
✓	C82	STAVNEZER, J., et al., "Immunoglobulin heavy-chain switching may be directed by prior induction of transcripts from constant-region genes", <i>Proc. Natl. Acad. Sci. (U.S.A.)</i> 85:7704-7708 (1988).	
✓	C83	STORB, U., et al., "Expression, Allelic Exclusion and Somatic Mutation of Mouse Immunoglobulin Kappa Genes", <i>Immunological Reviews</i> 89:85-102 (1986).	
✓	C84	STORB, U., "Immunoglobulin Gene Analysis in Transgenic Mice, in <i>Immunoglobulin Genes</i> , Academic Press Limited, pp. 303-326 (1989).	
✓	C85	SZUREK, P., et al., "Complete nucleotide sequence of the murine $\gamma$ 3 switch region and analysis of switch recombination in two $\gamma$ 3-expressing hybridomas", <i>J. Immunol.</i> 135:620-626 (1985).	
✓	C86	TAHARA, T., et al., "HLA antibody responses in HLA class I transgenic mice", <i>Immunogenetics</i> 32:351-360 (1990).	
✓	C87	TAKAI, T., et al., "Augmented Humoral and Anaphylactic Responses in Fc $\gamma$ R1I-deficient Mice", <i>Nature</i> 379:346-349 (1996).	
✓	C88	TAKI, S., et al., "Targeted Insertion of a Variable Region Gene into the Immunoglobulin Heavy Chain Locus", <i>Science</i> 262:1268-1271 (1993).	
✓	C89	TANAKA, T., et al., "An Antisense Oligonucleotide Complementary to a Sequence in Iy2b Increase $\gamma$ 2b Germline Transcripts, Stimulates B cell DNA Synthesis, and Inhibits Immunoglobulin Secretion", <i>The Journal of Experimental Medicine</i> 175:597-607 (1992).	
	C90	TAUSSIG, M.J., et al., "Regulation of immunoglobulin gene rearrangement and expression", <i>Immunology Today</i> 10:143-146 (1989).	
✓	C91	TAYLOR, L.D., et al., "Human immunoglobulin transgenes undergo rearrangement, somatic mutation and class switching in mice that lack endogenous IgM", <i>International Immunology</i> 6:579-591 (1994).	
✓	C92	THOMAS, K.R., and CAPECCHI, M.R., "Site-Directed Mutagenesis by Gene Targeting in Mouse Embryo-Derived Stem Cells", <i>Cell</i> 51:503-512 (1987).	
✓	C93	THOMAS, K.R., et al., "High Frequency Targeting of Genes to Specific Sites in the Mammalian Genome", <i>Cell</i> 44:419-428 (1986).	
✓	C94	TOMIZUKA, K., et al., "Double Trans-Chromosomal Mice: Maintenance of Two Individual Human Chromosome Fragments Containing Ig Heavy and Kappa Loci and Expression of Fully Human Antibodies", <i>Proc. Nat. Acad. Sci (USA)</i> 97:722-727 (2000)	
✓	C95	UHLMANN, E., and PEYMAN, A., "Antisense Oligonucleotides: A new therapeutic principle", <i>Chemical Reviews</i> 90:544-584 (1990).	
	C96	VLASOV, et al., "Arrest of immunoglobulin G mRNA translation in vitro with an alkylating antisense oligonucleotide derivative", <i>Chemical Abstracts</i> , p. 28, 112:229433X (1990).	
✓	C97	WAGNER, S.D., et al., "Antibodies generated from human immunoglobulin miniloci in transgenic mice.", <i>Nucleic Acids Res.</i> 1994 Apr 25;22(8):1389-93.	

Examiner Signature		Date Considered	6/3/05
--------------------	--	-----------------	--------

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 809. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English Language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. 1109726\_1



Substitute for form 1449A/PTO (Modified)				<b>Complete if Known</b>	
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)				Application Number	10/000,433
				Filing Date	November 30, 2001
				First Named Inventor	TOMIZUKA, Kazuma
				Group Art Unit	
				Examiner Name	
Sheet	7	of	7	Attorney Docket Number	014643-012110US (A-72018/455675-83)

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS		
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.
✓	C98	WEAVER, D., et al., "A Transgenic Immunoglobulin Mu Gene Prevents Rearrangement of Endogenous Genes", <i>Cell</i> 42:117-127 (1985).
✓	C99	WEISS, R., "Mice Making Human-Like Antibodies", <i>The Washington Post</i> , Apr. 28, 1994.
✓	C100	YAMAMURA, K.-I., et al., "Cell-type-specific and regulated expression of a human $\gamma 1$ heavy-chain immunoglobulin gene in transgenic mice", <i>Proc. Natl. Acad. Sci. USA</i> 83:2152-2156 (1986).
✓	C101	YANCOPOULOS, G.D., and ALT, F.W., "Developmentally Controlled and Tissue-Specific Expression of Unrearranged $V_H$ gene segments", <i>Cell</i> 40:271-281 (1985).
✓	C102	YANCOPOULOS, G.D., and ALT, F.W., "Regulation of the Assembly and Expression of Variable-Region Genes", <i>Ann. Rev. Immunol.</i> 4:339-368 (1986).
✓	C103	YASUI, H, et al., "Class switch from $\mu$ to $\delta$ is mediated by homologous recombination between $\sigma_\mu$ and $\Sigma_\delta$ sequences in human immunoglobulin gene loci", <i>Eur. J. Immunol.</i> 19:1399-1403 (1989).
✓	C104	ZIJLSTRA, M., et al., "Germ-line transmission of a disrupted $\beta_2$ -microglobulin gene produced by homologous recombination in embryonic stem cells", <i>Nature</i> 342:435-438 (1989).
✓	C105	ZIMMER, A., and GRUSS, P., "Production of chimaeric mice containing embryonic stem (ES) cells carrying a homoeobox <i>Hox 1.1</i> allele mutated by homologous recombination", <i>Nature</i> 338:150-153 (1989).

Examiner Signature		Date Considered	6/3/05
--------------------	--	-----------------	--------

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English Language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. 1109726\_1